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Consumption of Ultra-Processed Foods and Mortality: A National Prospective Cohort in Spain

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Abstract

Objective: To assess the prospective association between ultra-processed food consumption and all-cause mortality and to examine the effect of theoretical iso-caloric non-processed foods substitution.

Patients and Methods: A population-based cohort of 11,898 individuals (mean age 46.9 years, and 50.5% women) were selected from the ENRICA study, a representative sample of the noninstitutionalized Spanish population. Dietary information was collected by a validated computer-based dietary history and categorized according to their degree of processing using NOVA classification. Total mortality was obtained from the National Death Index. Follow-up lasted from baseline (2008-2010) to mortality date or December 31th, 2016, whichever was first. The association between quartiles of consumption of ultra-processed food and mortality was analyzed by Cox models adjusted for the main confounders. Restricted cubic-splines were used to assess dose-response relationships when using iso-caloric substitutions.

Results: Average consumption of ultra-processed food was 385 g/d (24.4% of the total energy intake). After a mean follow-up of 7.7 years (93,599 person-years), 440 deaths occurred. The hazard ratio (and 95% CI) for mortality in the highest versus the lowest quartile of ultra-processed food consumption was 1.44 (95% CI, 1.01-2.07; P trend=.03) in percent of energy and 1.46 (95% CI, 1.04-2.05; P trend=.03) in grams per day per kilogram. Isocaloric substitution of ultra-processed food with unprocessed or minimally processed foods was associated with a significant nonlinear decrease in mortality.

Conclusion: A higher consumption of ultra-processed food was associated with higher mortality in the general population. Furthermore, the theoretical iso-caloric substitution ultra-processed food by unprocessed or minimally processed foods would suppose a reduction of the mortality risk. If confirmed, these findings support the necessity of the development of new nutritional policies and guides at the national and international level.

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Affiliations continued at the end of this article.

Processing of food arose as a need to improve food availability, safety, digestibility, transportability, and storage life.[1,2] In the past decades, processing of food and food supplies have increased broadly providing ready-to-consume processed products that can be distributed all around the world.[3] Several food classifications have been proposed to quantify the nature and the extent of processed food intake when measuring it in populations.[4] The most extreme category corresponds to the ultra-processed foods, which are formulations made mostly or entirely from substances derived from foods and additives, with little if any whole food.[4]

Compared with the rest of the diet, ultra-processed foods often have a higher content of total fat, saturated fat, added sugars, and

salt, along with a low amount of fiber and low vitamin density.[5-7] In addition, they can contain neo-formed contaminants derived from physical, chemical, and biologic processes, along with substances from packaging and additives.[8,9] Moreover, epidemiologic evidence has demonstrated that ultra-processed food consumption is associated with poorer diet quality.[10,11] On the other hand, ultra-processed foods are highly palatable, habit-forming, convenient, microbiologically safe, affordable, and aggressively advertised and marketed.[12,13]

National household food purchase surveys and national dietary surveys have informed on ultra-processed food intake in some Western countries, such as the United States,[14] Canada,[15] New Zealand,[5] several European countries,[16,17] and some South American countries, such as Brazil,[18] and Chile.[19] It has been estimated that ultra-processed food intake is increasing, and it currently contributes 25%-50% of total energy intake.[20]

These shifts in dietary habits have been parallel to an increase in chronic diseases, beyond what was expected for a subject's chronological age,[21] and ultra-processed food consumption could have a role in this phenomenon.[22] Indeed, several longitudinal studies observed that ultra-processed food intake was associated with a higher incidence of dyslipidemia,[23] hypertension[24] and cancer.[25] Moreover, both cross-sectional[26, 27] and longitudinal studies[28] found a relationship with obesity.

Very recently, a cohort study conducted in France (the NutiriNet.Santé Study) assessed the association between ultra-processed food consumption and the risk of mortality among middle-aged adults (45 years old and older).[29] Participants were highly selected (mainly women, and more health conscious than the general population),[30] and all the information was based on electronic data. The authors found a positive relationship between ultra-processed food intake and the risk of mortality.

This study, conducted on a representative sample of the noninstitutionalized adult population of Spain, aimed to elucidate the association of ultra-processed food consumption as a whole with all-cause mortality. Moreover, we examined the effect of theoretical isocaloric nonprocessed foods substitution on this relationship. Information on food groups was also provided.

PATIENTS AND METHODS

Study Population
Data were taken from the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA), whose methods have been reported elsewhere.[31] In brief, 12,948 individuals were selected between June 2008 and October 2010 by stratified cluster sampling to ensure that they were a representative sample of the non-institutionalized population of Spain age 18 years and older. First, the sample was stratified by province and size of the municipality. Second, clusters were selected randomly in 2 stages: municipalities and census sections. Finally, the households within each section were selected by random telephone dialing. Participants in the households were selected proportionally to the sex and age distribution of the Spanish population.

Trained and certified personnel collected information in 3 sequential stages: (1) a telephone interview to obtain data on sociodemographic factors, health behaviors, self-rated health, and morbidity; (2) a first home visit to collect blood and urine samples, and (3) a second home visit to perform a physical examination, and to obtain habitual diet by using a computerized dietary history. More information about the sample collection process has been already published.[31]

Written informed consent was obtained from all participants. The study was approved by the Clinical Research Ethics Committees of the La Paz University Hospital in Madrid and the Hospital Clinic in Barcelona (Spain).

Dietary Assessment and Extent and Purpose of Processing of Foods
A validated computer-based dietary history (DH-ENRICA) was used to ascertain the participant's habitual consumption of different

foods. The DH-ENRICA is a computerized questionnaire administered by a trained interviewer; it includes 880 foods that can be cooked in 29 different ways and 184 recipes for dishes commonly eaten in Spain or typical of each region. Taking into account the weekly frequency of consumption of each food and the seasonal intake, this dietary history provides an estimate in daily grams of foods that represent the average intake during the preceding year. More details about DH-ENRICA and dietary information collection have been published in Guallar-Castillon et al.[32] Standard food composition tables from Spain and other countries allowed calculation of the amount of energy and nutrient intake.[32]

All recorded food items were classified according to the NOVA food classification based on the extent and purpose of industrial food processing.[6] The rationale underlying the NOVA food classification, the detailed definition of each NOVA food group, and examples of food items classified in each group have been shown elsewhere.[4,18,33] Foods were classified into 4 groups: (1) "unprocessed or minimally processed foods," defined as foods that are of plant or of animal origin consumed shortly after harvesting, gathering, slaughtering, or husbanding, or foods that are altered in ways that do not add or introduce any substances, but that might involve subtracting parts of the food; (2) "processed culinary ingredients," defined as food products extracted and refined from elements of foods, such as plant oils, animal fats, starches, and sugar, or obtained from nature (eg, salt) that are normally not consumed by themselves; (3) "processed foods" that are made by adding salt or sugar (or other substances of culinary use such as oil or vinegar) to unprocessed or minimally processed foods, in order to preserve them or to enhance their palatability; and (4) "ultra-processed foods," which are those that were formulated mostly or entirely from substances derived from foods, with little or even no whole food content. These ingredients include modified starches, hydrogenated oils, protein isolates, and additives whose purpose is to imitate sensorial qualities of unprocessed or minimally processed foods and

their culinary preparations, or to disguise undesirable qualities of the final product, such as colorants, flavorings, nonsugar sweeteners, emulsifiers, humectants, sequestrants, and firming, bulking, defoaming, anticaking, and glazing agents. The full list of the recorded foods and their NOVA classification is shown in the Supplemental Appendix (available online at http://www.mayoclinicproceedings.org). It should be noted that a food group can have foods that can be classified in different NOVA categories. For example, in the food group "yogurts and fermented milks," natural skimmed fermented milk, natural fermented whole milk, natural skimmed yogurt, natural whole yogurt, and kefir were considered in group 1 as "unprocessed or minimally processed foods," whereas skimmed fermented milk with fruits, whole fermented milk with fruits, skimmed flavored yogurt, skimmed yogurt with fruits, natural skimmed yogurt with sweetener, whole flavored yogurt, whole yogurt with fruits, natural whole yogurt with sweetener, whole drinking/liquid yogurt, whole drinking/liquid yogurt with fruit, natural drinking/liquid yogurt with sweetener, and natural Greek yogurt were considered in group 4 as "ultra-processed foods."

Mortality Ascertainment

All-cause mortality from baseline in 2008-2010 to the end of follow-up on December 31, 2016, was obtained for 99.9% of the cohort. A computerized search was performed in the Spanish National Death Index, which contains information on the vital status of all residents in Spain. Censoring was set at the date of death or at the end of follow-up, whichever occurred first.

Covariates

Sex, age, educational level (no formal education, primary, and secondary or higher) were recorded. Individuals also reported whether they lived alone; whether they were current, former, or never smokers; and whether they were former drinkers. Physical activity was recorded using the European Prospective Investigation into Cancer and Nutrition cohort questionnaire. A Physical Activity

Index was based on a cross-tabulation of occupational, household, and recreational activities, categorizing individuals into 4 levels of activity: inactive, moderately inactive, moderately active, and active.[34] Time spent watching television and time devoted to other sedentary activities (computer use, reading, commuting, and listening to music) were also registered in hours per week.[35] Finally, the amount of medication per day and the presence of chronic conditions diagnosed by a physician (chronic respiratory disease, coronary heart disease, stroke, heart failure, osteoarthritis, cancer, and depression requiring treatment) were also self-reported.

Statistical Analysis

Of the 12,948 study participants, 1050 of them were excluded because of inconsistent dietary data (total daily energy intake outside the range of 800-5000 kcal in men, or 500-4000 in women; n=60), missing information on diet (n=887), or covariates (n=103). Thus, the analyses were conducted with 11,898 individuals (5890 men and 6008 women).

For each participant, the proportion of total energy from ultra-processed foods was calculated, and the total sample was divided into quartiles (cutoff points were set at 14.1%, 23.0%, and 33.1%). Cox proportional hazards models were used to assess the association between quartiles of ultra-processed food intake (in percentage of total energy intake) and mortality. The first quartile (lowest intake) was used as the reference. Analyses were weighted to account for the complex sampling design, and the variances were also corrected to calculate appropriate 95% CIs. Linear trend was calculated using quartiles of ultra-processed food as a continuous variable. Schoenfeld residuals were plotted against time to detect violations of the proportional hazard assumption. Finally, ultra-proceed foods were also expressed in grams per day per kilogram weight of the participant. Bodyweight was assessed using electronic scales (model Seca 841; Seca Deutschland, Hamburg, Germany; precision to 0.1 kg).

Cox models were built with 4 successive levels of additional adjustments: model 1 was adjusted for age and sex; model 2 was adjusted for socioeconomic factors (educational level and living alone); model 3 was adjusted for lifestyle factors (smoking status, former drinker, physical activity, time watching television, and time devoted to other sedentary activities), and model 4 was adjusted for clinical factors (number of medications per day and presence of chronic conditions). We also performed several sensitivity analyses.

We built isocaloric substitution models that simultaneously included energy intake, the percentages of energy derived from ultra-processed foods, from processed culinary ingredients, and processed food or unprocessed or minimally processed foods, as appropriate, and other potential confounding variables. Nonlinear relations were identified using restricted cubic spline analyses with 3 knots or inflection points placed at the 10th, 50th, and 90th percentiles. The coefficients from these models can be interpreted as the estimated association of substituting a certain percentage of energy from ultra-processed foods with the equivalent energy from processed foods or unprocessed or minimally processed foods while holding constant the intake of total energy and the energy from the corresponding non-replaced NOVA groups.[36]

Secondary analyses were performed for nutrient intake from ultra-processed foods (as a percentage of total energy or as caloric density), considering the main food groups contributing to ultra-processed food intake. These variables were divided into quartiles, tertiles, or median according to the number of participants with intake in the corresponding categories and always using the lowest category as a reference. Analyses were performed with Stata software version 14 for Windows (StataCorp LP), and statistical significance was set at $P<.05$. The survey command was used in the analyses to account for the complex sampling.

RESULTS

The cohort comprised 11,898 subjects (mean age, 46.9 years; 50.5% female) who had an average consumption of ultra-processed

food of 385 g/d, corresponding to 24.4% of the total energy intake. Those in the first quartile of ultra-processed foods consumed a mean of 8.7% (mean, 156 g), versus 42.8% (mean, 641 g) consumed by those in the highest quartile (Supplemental Figure 1, Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). After a mean of 7.7 years and 93,599 person-years followed up, 440 deaths occurred.

Subjects that consumed more ultra-processed foods also ingested more energy, were younger, were more frequently current smokers, were more educated, had a higher activity index, watched fewer hours of television but dedicated more time to other sedentary activities, took less medication per day, and had lower prevalence of stroke, heart failure, osteoarthritis, and cancer but higher rates of depression (Table 1). They also had a higher intake of carbohydrates, simple sugars, total fat, saturated fatty acids, polyunsaturated fatty acids, trans fatty acids, and sodium (Supplemental Table 1, Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). The main food groups contributing to ultra-processed food intake were meat and meat products (17.1%), cakes and pastries (13.6%), cookies (9.2%), yogurts and fermented milk (8.8%), jams and confectionery (7.4%), and precooked dishes (7.1%). These food groups had a different relative contribution among ultra-processed quartiles (Supplemental Table 2).

In all models, participants in the highest quartile of ultra-processed food intake had higher mortality risk when compared with those in the lowest quartile; in model 4, the hazard ratio (HR) for mortality was 1.44 (95% CI, 1.01-2.07; P for trend=.03). The corresponding mortality risk when ultra-processed food consumption was expressed in grams per day per kilogram weight was 1.46 (95% CI, 1.04-2.05; P for trend=.03; Table 2). Sensitivity analyses provided similar results (Supplemental Table 3, Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

In model 4, the hazard ratio of the isocaloric substitution of ultra-processed foods with processed foods was less than 1 but did not achieve statistical significance (Figure A). However, when replaced with unprocessed or minimally processed foods, an inverse and nonlinear dose-response was observed (P for nonlinearity=.04), starting to be significant when replacing 8.2% of ultra-processed food consumption (Figure B).

When comparing the highest versus the lowest quartile of nutrients intake from ultra-processed foods, consumption of total carbohydrates, simple sugars, saturated fatty acids, and trans fatty acids contributed the most to increased mortality risk, although only trans fatty acids reached statistical significance (HR, 1.39; 95% CI, 1.00-1.92; P for trend=.05; Supplemental Figure 2, Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). When analyzing ultra-processed food consumption by food groups, the intake of yogurts and fermented milks (those classified as ultra-processed), cakes and pastries, and cookies contributed the most to an increased mortality risk, but it only reached statistical significance for yogurts and fermented milks (HR, 1.37; 95% CI, 1.02-1.86) with a nonsignificant trend (P for linear trend=.09). The other groups of ultra-processed foods (breads, breakfast cereals, dairy desserts, meat and meat products, jams and confectionery, sauces and dressings, soft drinks, packaged fruit juices, and nectars) were not associated with increased risk of mortality. (Supplemental Figure 3, Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

Principal Findings

In this prospective study, based on a representative sample of the noninstitutionalized adult population of Spain, an increased intake of ultra-processed food was associated with higher mortality after 7.7 years of follow-up. Participants in which ultra-processed food intake contributed more than 33% of total energy intake had a 44% higher all-cause mortality risk compared with those in whom ultra-processed food intake contributed up to 14% of total energy intake.

TABLE 1. Baseline Characteristics of the Cohort Participants According to Quartiles of Ultra-processed Food Consumption (% of Energy) in the ENRICA Study (2008-2010)

Characteristics	All subjects (N=11,898)	Quartiles of ultra-processed food consumption (% total energy)[a]				P for linear trend
		Q1, lowest (n=2976)	Q2 (n=2974)	Q3 (n=2974)	Q4, highest (n=2974)	
Total energy (kcal/d), mean ± SE	2173.9 ± 9.0	1970.0 ± 13.3	2078.0 ± 13.4	2263.5 ± 17.4	2378.9 ± 15.8	<.001
Ultra-processed food consumption (% of energy), mean ± SE	24.47 ± 0.17	8.68 ± 0.08	18.60 ± 0.05	27.82 ± 0.06	42.83 ± 0.19	<.001
Ultra-processed food consumption (g/d), mean ± SE	384.70 ± 4.30	155.50 ± 2.90	304.70 ± 5.10	436.90 ± 6.20	641.20 ± 9.00	<.001
Weight (kg), mean ± SE	73.80 ± 0.20	74.60 ± 0.30	74.10 ± 0.40	73.60 ± 0.30	73.00 ± 0.40	<.001
Ultra-processed food consumption (grams per d/weight), mean ± SE	5.34 ± 0.06	2.12 ± 0.04	4.18 ± 0.07	6.08 ± 0.09	9.01 ± 0.13	<.001
Women (%)	50.5%	49.1%	51.8%	50.1%	51.0%	.39
Age (y), mean ± SE	46.9 ± 0.27	54.93 ± 0.40	49.40 ± 0.38	44.60 ± 0.44	38.79 ± 0.40	<.001
Educational level, (%)						<.001
No formal education	30.0%	40.5%	31.2%	26.1%	22.1%	
Primary	42.0%	32.6%	40.5%	45.1%	49.7%	
Secondary or higher	28.1%	26.9%	28.4%	28.8%	28.2%	
Living alone (%)	7.8%	9.0%	8.8%	7.1%	6.2%	<.001
Smoking status (%)						<.001
Current smoker	27.5%	24.7%	27.0%	28.4%	30.0%	
Former smoker	24.7%	30.8%	25.7%	22.9%	19.6%	
Never smoker	47.8%	44.6%	47.3%	48.7%	50.4%	
Former drinker (%)	5.5%	5.3%	5.5%	5.8%	5.4%	.93
Physical activity index (%)						<.001
Inactive	27.7%	33.2%	28.6%	25.6%	23.4%	
Moderately inactive	33.8%	35.2%	33.3%	33.3%	33.3%	
Moderately active	23.0%	20.1%	23.7%	24.2%	23.9%	
Active	15.6%	11.6%	14.4%	17.0%	19.4%	
Time watching television (h/wk), mean ± SE	13.67 ± 0.12	14.43 ± 0.24	13.85 ± 0.23	13.35 ± 0.21	13.16 ± 0.23	<.001
Time devoted to other sedentary activities (h/wk), mean ± SE	15.52 ± 0.16	13.69 ± 0.29	15.11 ± 0.26	16.24 ± 0.33	17.03 ± 0.28	<.001
Number of medications per day, mean ± SE	0.84 ± 0.02	1.18 ± 0.04	0.95 ± 0.04	0.71 ± 0.03	0.53 ± 0.03	<.001
Chronic conditions (%)						
Chronic respiratory disease	6.4%	6.3%	6.8%	6.5%	5.9%	.72
Coronary heart disease	0.6%	0.9%	0.6%	0.5%	0.4%	.15
Stroke	0.4%	0.7%	0.6%	0.2%	0.3%	.03
Heart failure	1.5%	1.7%	1.9%	1.1%	1.1%	.03
Osteoarthritis	20.7%	28.2%	24.6%	17.2%	12.9%	<.001
Cancer	1.0%	1.6%	0.9%	0.9%	0.7%	.01
Depression	6.6%	6.4%	7.3%	5.4%	7.5%	.02

[a]Interquartiles ranges are: 0%-14.08% for Q1; 14.09%-23.00% for Q2; 23.01%-33.14% for Q3; and 33.15%-100% for Q4.

Interpretation and Comparison with Other Studies

To our knowledge, this is the first prospective epidemiologic study performed in a large and representative national cohort that evaluated the association between ultra-processed food consumption (as a whole) and risk for all-cause mortality in participants age 18 years and older.

TABLE 2. Mortality risk according to ultra-processed food consumption quartiles in the ENRICA Study (N=11,898)[a]

	Q1 (lowest)	Q2	Q3	Q4 (highest)	P for linear trend
Quartiles of ultra-processed food consumption (% energy)					
n	2976	2974	2974	2974	
Deaths	158	105	103	74	
Person-years	23,308	23,378	23,438	23,475	
Model 1, HR (95% CI)[a]	1 (Reference)	0.97 (0.73-1.30)	1.28 (0.95-1.73)	1.44 (1.00-2.06)	.02
Model 2, HR (95% CI)	1 (Reference)	0.98 (0.73-1.31)	1.30 (0.96-1.74)	1.51 (1.05-2.16)	.01
Model 3, HR (95% CI)	1 (Reference)	0.94 (0.70-1.26)	1.25 (0.93-1.68)	1.42 (0.99-2.04)	.03
Model 4, HR (95% CI)	1 (Reference)	0.91 (0.67-1.23)	1.23 (0.91-1.67)	1.44 (1.01-2.07)	.03
Quartiles of ultra-processed food consumption (grams per d/weight)					
n	2951	2950	2950	2950	
Deaths	148	125	98	59	
Person-years	23,181	23,183	23,222	23,281	
Model 1, HR (95% CI)[b]	1 (Reference)	1.07 (0.81-1.41)	1.21 (0.91-1.62)	1.48 (1.05-2.10)	.02
Model 2, HR (95% CI)	1 (Reference)	1.08 (0.82-1.43)	1.23 (0.93-1.65)	1.39 (0.97-1.99)	.01
Model 3, HR (95% CI)	1 (Reference)	1.08 (0.82-1.43)	1.19 (0.89-1.60)	1.48 (1.06-2.07)	.02
Model 4, HR (95% CI)	1 (Reference)	1.08 (0.81-1.44)	1.21 (0.89-1.64)	1.46 (1.04-2.05)	.03

[a]HR = hazard ratio.

[b]Model 1: adjusted for sex and age. Model 2: adjusted as in model 1 plus, educational level, and living alone. Model 3: adjusted as in model 2 plus, smoking status, former drinker, physical activity index, time watching television, and time devoted to other sedentary activities. Model 4: adjusted as in model 3 plus the number of medications per day, and specific chronic conditions diagnosed by a physician (chronic respiratory disease, coronary heart disease, stroke, heart failure, osteoarthritis, cancer, and depression).

Our results are in line with those obtained in the NutriNet-Santé Study.[29] According to our results, the strength of the association is probably higher than that presented in the NutriNet-Santé Study. This is especially important because young generations are increasing their consumption of ultra-processed food, and its consequences will be seen in the future.
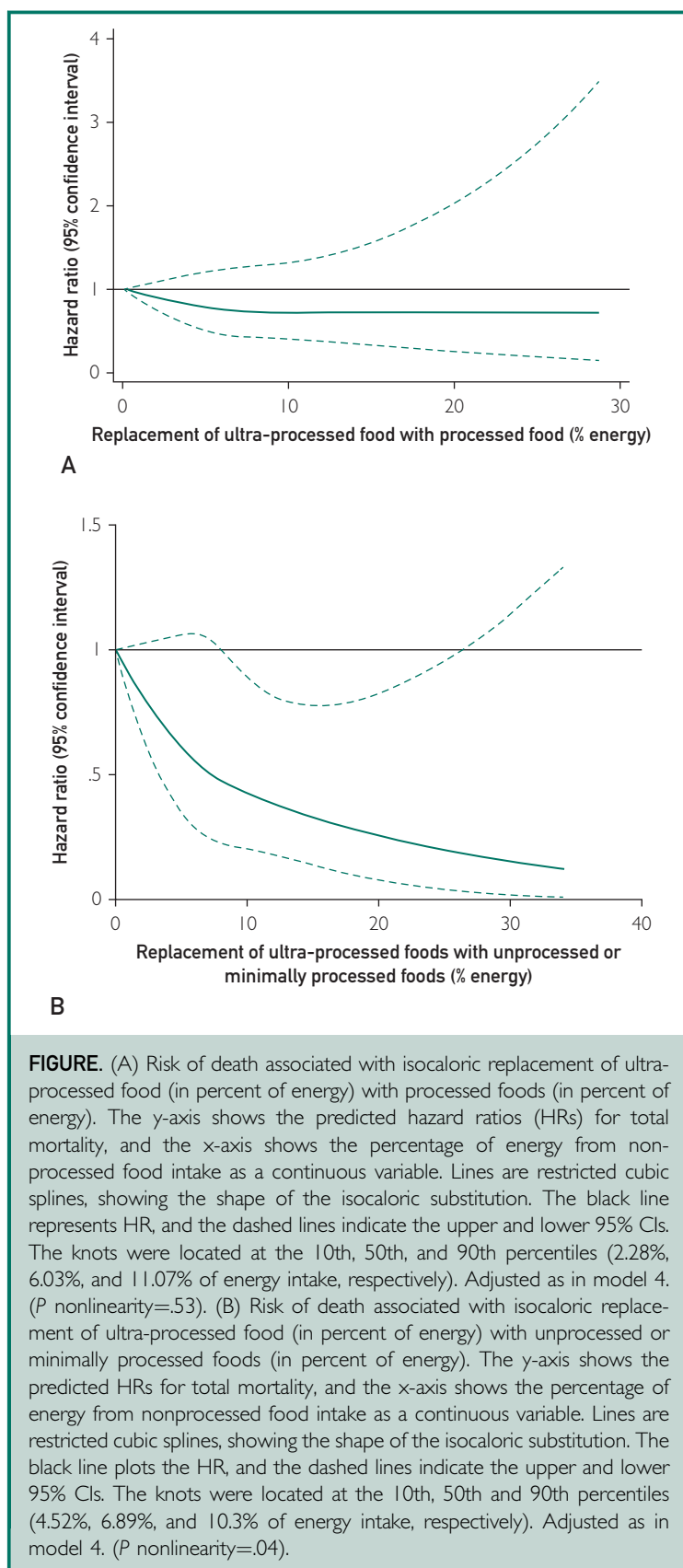
In Spain, consumption of ultra-processed food intake was 24.4% of total dietary calories, being consistent with previous data from the Data Food Networking Database databank showing that 20.3% of total purchased dietary energy came from ultra-processed foods.[27] Spain is a country with low ultra-processed food consumption when compared with other Western countries, such as Canada (61.7%),[15] the United States (57.9%),[14] the United Kingdom (53%),[37] and France (35.9%),[16] or developing countries such as Brazil (29.6%).[18] This could be explained as cooking at home being part of the Mediterranean diet, which is also rich in unprocessed or minimally processed foods.[38-40] However, it is also known that the Spanish population has been drifting away from this traditional pattern to adopt a less healthy diet,[41] especially among young people,[42] supporting the estimates that ultra-processed foods consumption will continue to increase.[20]

The association of some groups of ultra-processed foods with mortality has been studied previously. In the United States, positive associations were found between fast food and sugar-sweetened beverage consumption and mortality.[43] In addition, a recent meta-analysis showed a nonlinear 7% higher risk with an increased intake of sugar-sweetened beverages up to 250 mL/d.[42] An increased risk of mortality has also been shown with meats and processed meats.[44-46] Regarding dairy products, studies showed controversial results. Although a recent meta-analysis of 29 prospective cohort studies demonstrated neutral associations between milk and dairy products and mortality; there was not a distinction between processed and ultra-processed foods.[47] In the present analysis, sugared, sweetened, flavored, and additive-added dairy products were considered as ultra-

processed. On the contrary, milk, plain yogurts, and fresh and cured cheeses were not included in this category. Our results suggest that the intake of ultra-processed yogurts and fermented milks is associated with increased mortality, reinforcing the idea of considering the extent of processing when studying dairy product. Moreover, the obtained isocaloric replacement results are supported by different studies that used national household data to estimate the contribution of dietary trends for risk of cardiovascular disease and all-cause mortality. In the United Kingdom, a reduction of 13% of cardiovascular disease mortality was projected by 2030 if dietary intake of ultra-processed and processed foods were entirely replaced with unprocessed or minimally processed foods.[48] In Brazil, using a similar approach, an 11% cardiovascular mortality reduction was estimated if ultra-processed foods were reduced by 50% and substituted with unprocessed or minimally processed foods, plus an additional 50% reduction in processed culinary ingredients.[49]

How ultra-processed food consumption increases the risk of all-cause mortality could depend on a number of factors. Ultra-processed foods have a high-energy density that is less satiating, highly accessible[6,33,50] and prone to causing inadvertent overconsumption, which has also been associated with mortality.[51] Moreover, ultra-processed foods are industrial formulations containing high quantities of saturated fatty acid, trans fatty acids, hydrogenated oils, starches, free sugars, and salt, plus food additives used to imitate the sensory qualities of natural foods, or to disguise undesirable qualities of the final product, such as colorants, flavorings, artificial sweeteners, and emulsifiers.[5,9] Harmful effects of some of these nutritional compounds have been studied widely. Trans fatty acid intake has been related to an increase in all-cause mortality risk in several populations,[52, 53] as has total sugar intake.[54] The association of saturated fatty acid intake and mortality is controversial,[55,56] highlighting the need to take into account the food sources of saturated fatty acids.[57] In addition, a meta-analysis of 23 cohort studies found a U-shaped association

FIGURE. (A) Risk of death associated with isocaloric replacement of ultra-processed food (in percent of energy) with processed foods (in percent of energy). The y-axis shows the predicted hazard ratios (HRs) for total mortality, and the x-axis shows the percentage of energy from non-processed food intake as a continuous variable. Lines are restricted cubic splines, showing the shape of the isocaloric substitution. The black line represents HR, and the dashed lines indicate the upper and lower 95% CIs. The knots were located at the 10th, 50th, and 90th percentiles (2.28%, 6.03%, and 11.07% of energy intake, respectively). Adjusted as in model 4. (P nonlinearity=.53). (B) Risk of death associated with isocaloric replacement of ultra-processed food (in percent of energy) with unprocessed or minimally processed foods (in percent of energy). The y-axis shows the predicted HRs for total mortality, and the x-axis shows the percentage of energy from nonprocessed food intake as a continuous variable. Lines are restricted cubic splines, showing the shape of the isocaloric substitution. The black line plots the HR, and the dashed lines indicate the upper and lower 95% CIs. The knots were located at the 10th, 50th and 90th percentiles (4.52%, 6.89%, and 10.3% of energy intake, respectively). Adjusted as in model 4. (P nonlinearity=.04).

between sodium intake and mortality.[58] In our cohort, the separate analysis of these nutrients from ultra-processed foods increase the risk of all-cause mortality, although only trans fatty acids reached a significant association. These results support the application of food processing classification beyond conventional food classifications and the report on single nutrients[5]; because the concept of ultra-processed foods does not just focus attention on these "traditional" harmful nutrients but to a wider range of food additives contained in this type of foods. Although food additive safety is rigorously controlled by the European authorities,[59] the detrimental health effects in the long term and the potential interaction consequences between the different compounds are largely unknown.[9] Finally, consumption of ultra-processed foods was also associated with a poorer diet quality (with less consumption of fiber, fruit, and vegetables)[10, 11] and unhealthy lifestyle (smoking and sedentary behaviors),[16,60] all contributing to increased mortality.[13,46,61] However, further mechanistic studies to know how and to which extent ultra-processed foods could affect health should be performed.

Strengths and Limitations of the Study
This study has some strengths, including its prospective design and a relatively large sample size representative of the adult Spanish population, which broadens the generalization of the results. Food consumption was collected in detail with a validated dietary history including a wide variety of foods and their cooking methods.[32] Finally, many confounding factors were considered in the analysis; however, there are some limitations. First, dietary information was obtained only at baseline, assuming no time changes in dietary intake and probably underestimating the real impact of ultra-processed foods on mortality. Second, although there was a consensus between authors about NOVA classification of the foods obtained by the dietary history, some degree of misclassification among ultra-processed food categories cannot be ruled out. In this regard, we were aware that NOVA classification has been criticized (mainly because of the broad definition of ultra-processed food),[62] but it is the most used and recommended for classifying ultra-processed foods in public health nutrition.[20] Third, the relatively low number of deaths precluded meaningful analyses by specific causes of death. Last, a certain degree of residual confounding can still exist, and non-differential misclassification affecting both, exposure and disease, can still operate, leading to a dilution bias of the true effect.

Conclusions and Policy Implications
In conclusion, an increased intake of ultra-processed food was associated with a higher risk of mortality. Moreover, the theoretical isocaloric substitution of ultra-processed food by unprocessed or minimally processed foods would suppose a reduction of the mortality risk. These results need to be confirmed by other large-scale, population-based, prospective studies in different countries and settings. Further study is also needed to identify the specific foods that mostly account for this association and to investigate possible relationships with specific causes of death. However, our findings support the epidemiologic evidence about the harmful effects of ultra-processed foods, and thus, the necessity to implement actions, such as the development of new nutritional policies and guides, both for the population and the industry. Ultra-processed food intake can be considered one of the major challenges that governments will have to face in the next decades, and one of the main opportunities for nutritional prevention.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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